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Microbial β-Glucosidase: Sources, Production and Applications

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Abstract Cellulose is the most abundant biopolymer in biosphere and the major constituent of plant biomass. Cellulose polymer is made up of β-glucose units linked by β-glucosidic bonds. Cellulase is an enzymatic system that catalyzes the hydrolysis of cellulose polymer to glucose monomers. This enzymatic system consists of three individual enzymes namely endoglucanase, exoglucanase and β-glucosidase which act synergistically to degrade cellulose molecules into glucose. Cellulases are produced by bacteria, fungi, plants, and animals and used in many industrial applications such as textile industries, laundry and detergent industries, paper and pulp industry, animal feeds, and biofuels production. β-Glucosidase is a diverse group of enzymes with wide distribution in bacteria, fungi, plants and animals and has the potential to be utilized in various biotechnological processes such as biofuel production, isoflavone hydrolysis, flavor enhancement and alkyl/aryl β-D-glucoside and oligosaccharides synthesis. Thus, there is increased demand of β-glucosidase production from microbial sources under profitable industrial conditions. In this review, β-glucosidase classification, localization, and mechanism of action will be described. Subsequently, the various sources of β-glucosidase for industrial sector will be discussed. Moreover, Fermentation methods and various parameters affecting β-glucosidase production will be highlighted on the light of recent findings of different researchers. Finally, β-glucosidase applications in biofuel production, flavors enhancement, isoflavones hydrolysis, cassava detoxification and oligosaccharide synthesis will be described.

Keywords: *cellulose, glycoside hydrolase, cellulase, β-glucosidase, biofuel, transglycosylation*

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1. Introduction

Cellulose is the most abundant organic biopolymer in biosphere and the major constituent of lignocellulosic material making up to 35-50% of plant biomass. Hemicellulose and lignin are the other two constituents making up to 20-35% and 10-15%, respectively. This biomass is known to be renewable with annual production of approximately 1 x 10^{10} tons, sustainable and cheap source of energy [1-8]. Biomass is the fourth among world energy sources after coal, fossil fuel and natural gas, providing 10-14% of the total energy [9,10]. Lignocellulosic material can be converted into numerous valuable organic compounds such as sugar, bioethanol, amino acids, organic acids and food additives. It can also be used as substrate for production of many industrially important enzymes [11,12,13,14,15]. Cellulose is a linear polymer of anhydro-β-D-glucose unit linked by β-(1-4) O-glycosidic bonds ranging from 800-10000 units forming a chain with average molecular weight of 100000 Da [4,7,16,17,18]. Cellulose chains are stabilized by intra- and intermolecular hydrogen bonds and Van Der Walls forces [19,20]. Usually cellulose polymer has two regions: crystalline region recalcitrant to enzymatic hydrolysis and amorphous region easily accessible to enzymatic hydrolysis [21,22,23]. To be utilized in various industrial applications e.g., bioethanol production, cellulose must first be broken down to simple fermentable sugar i.e., glucose. In nature, cellulose degradation is mediated by combined action of three individual enzymes named as endoglucanase (1,4-β-D-glucan hydrolase; EC 3.2.1.4), exoglucanase (1,4-β-D-glucan glucohydrolase EC 3.2.1.74) and β-glucosidase (β-D-glucoside glucohydrolase EC3.2.1.21) [24,25,26,27]. To begin with, endoglucanase randomly attacks and hydrolyzes glucosidic bonds in the interior of the molecule especially in the amorphous regions generating oligosaccharides chains of different length. This is followed by exoglucanase/cellobiohydrolase that processively hydrolyzes these chains at their reducing and nonreducing ends releasing glucose, cellobiose, and short oligosaccaharides. These two enzymes act synergistically and are usually inhibited by cellobiose. Finally, β-glucosidase breaks down cellobiose and short oligosaccharides into glucose units thus eliminating cellobiose inhibitions on endoglucanase and cellobiohydrolases [22,24,28-33]. These three enzymes are collectively referred to as cellulase enzyme and produced by bacteria, fungi, protozoa, plants, and animals [26,34,35,36]. Cellulase enzymes collectively are used in various industries such as laundry and detergents industry, textile industry, paper and pulp industry, animals feed, food industry etc. [18,28,35-40].

β-Glucosidase is an ubiquitous enzyme produced by all life domains: bacteria, fungi, plants and animals including noncellulolytic organisms such as human [24]. It hydrolyzes β-D-glucosidic bonds of various compounds comprising of alkyl-β-D-glucosides, aryl-β-D-glucosides, cyanogenic glucosides, disaccharides and short chain oligosaccharides liberating glucose from their nonreducing end, in addition, some novel β-glucosidases with β-galactosidase and β-xylosidase activity have also been reported [41,42]. Under certain circumstances, β-glucosidase also catalyzes synthetic reactions of oligosaccharides/glycosides [43,44,45]. This synthetic activity is brought about in two ways: either through reverse hydrolysis or transglycosylation. In reverse hydrolysis reaction, lowering water activity, trapping of product or high substrate concentration results in a shift of reaction equilibrium toward synthesis through "reverse hydrolysis". This reaction is under thermodynamic control. In transglycosylation reaction, donor glycoside is hydrolyzed by the enzyme resulting in enzyme-glycosyl intermediate which is in turn attacked by a nucleophile other than water such monosaccharide, disaccharide, aryl-amino, alkyl-alcohol or monoterpene alcohol to yield a new elongated product. This reaction is under the kinetic control [44,46,47].

β-Glucosidase plays fundamental roles in many physiological processes [48,49]. For instance, in plants, it is involved in defense [50,51], β-glucan chain synthesis and cell wall metabolism [52,53], lignification [54,55], phytohormone activation [56,57], secondary metabolism [58,59], and fruit ripening [60,61]. In microorganisms, it plays roles in cellulose hydrolysis, carbon recycling and cellulase gene induction [62,63,64,65]. In mammals, β-glucosidase is involved in hydrolysis of glucosyl ceramides and in humans its defect causes Gaucher's disease [66, 67].

β-Glucosidases, particularly those derived from microbial sources, have the potential to be used in many biotechnological processes such as bioethanol production [68,69], improvement of the aroma in wine and fruit juices industry through release of the aromatic compounds from flavorless glycosides [70]. They are also used to hydrolyze isoflavone glycosides thus increasing their absorption from small intestine positively affecting human health [71,72,73]. β-Glucosidases can also be utilized for detoxification of cassava [74,75,76], and deinking of waste paper [77,78]. Based on synthetic activity, β-glucosidase is utilized in biosynthesis of oligosaccharides and alkyl glycosides [79,80,81,82,83]. These compounds have wide range of uses in medical sciences as therapeutics agents, diagnostics tools, and as growth promoters for probiotics bacteria [84]. Alkyl glycosides have anionic surfactant properties and can be used as antimicrobial agents [85,86,87], and in pharmaceutical, cosmetics, detergent and foods industries [83].

β-Glucosidases are produced by microorganisms in low quantities [88], and inhibited by their end product i.e., glucose [89], resulting in accumulation of cellobiose during cellulolysis which in turn inhibits both endo-/exo-glucanase. β-Glucosidase is therefore considered to be the key enzyme in determining the cellulase efficiency and the bottle neck in bioethanol production through biomass conversions [90,91,92]. Researchers are focusing on finding or developing microorganisms with high β-glucosidase productivity and/or β-glucosidase with high glucose tolerance, thermostability and catalytic efficiency.

In this review, we describe β-glucosidases classification, localization, and mechanism of actions. Further, the microbial sources of β-glucosidases, production methods along with parameters affecting their production will be discussed thoroughly. Finally, biotechnological applications of β-glucosidases such as bioethanol production, flavors enhancement of wine and fruit juices, among other potential applications, will also be highlighted.

1.1. β-Glucosidase Classification

β-Glucosidase cleaves β-D-glucosidic bonds from a variety of compounds releasing glucose as the end product. Thus, differing greatly in their substrate specificity particularly with regard to the aglycone moiety making their classification a challenge [44]. The two widely accepted methods for their classification are: 1) classification based on substrate specificity and 2) classification based on nucleotide sequences identity and hydrophobic cluster analysis [43]. Based on substrates specificity, β-glucosidases are categorized in three classes: 1) aryl-β-glucosidases hydrolyzing only aryl-β-glucoside linkage, 2) cellobiases hydrolyzing only cellobiose, and 3) broad substrate specificity β-glucosidase hydrolyzing wide range of substrates with different bonds such as β(1→4), β(1→3), β(1→6), α(1→4), α(1→3), and α(1→6) linkage. Most of the reported microbial β-glucosidases show broad substrate specificity [46,93,94]. Based on sequence identity and hydrophobic cluster analysis, β-glucosidases are placed in Glycoside Hydrolase (GH) family 1 and family 3 as in Carbohydrate active enZyme database "CaZy" [49,95,96,97]. β-Glucosidases belonging to GH family 1 are reported from archeabacteria, plants and animals whereas β-glucosidases belonging to GH family 3 are from bacteria, fungi and yeast, although β-glucosidase can also be found in family 5, 9, 30 and 116 [43,44,46,73].

1.2. Localization of β-Glucosidases

Microbial β-glucosidases are localized as intracellular, extracellular, or cell-bound enzymes [98,99]. Generally β-glucosidases belonging to GH 3 are localized as extracellular or cell-bound enzymes whilst those belonging to GH 1 are predominately intracellular enzymes [100,101]. Some Fungal species such as *Trichoderma reesei* are known to synthesize extracellular, intracellular and cell-bound β-glucosidase [102]. Majority of the reported fungal β-glucosidases are extracellular and belong to GH 3 whereas majority of the reported bacterial β-glucosidases are intracellular and belonging to GH 1[44]. For instance, extracellular and cell-bound β-glucosidase from *Aspergillus kawachii* [92], an intracellular β-glucosidase from the bacterium *Baciulus circulans* subsp. *Alkalophilus* [103], and extracellular β-glucosidase from unidentified bacterial isolate M+, and *Bacillus subtilis* strain [104,105] have all been reported. Extracellular, intracellular and cell bound β-glucosidase in yeast have also been identified [106,107,108].

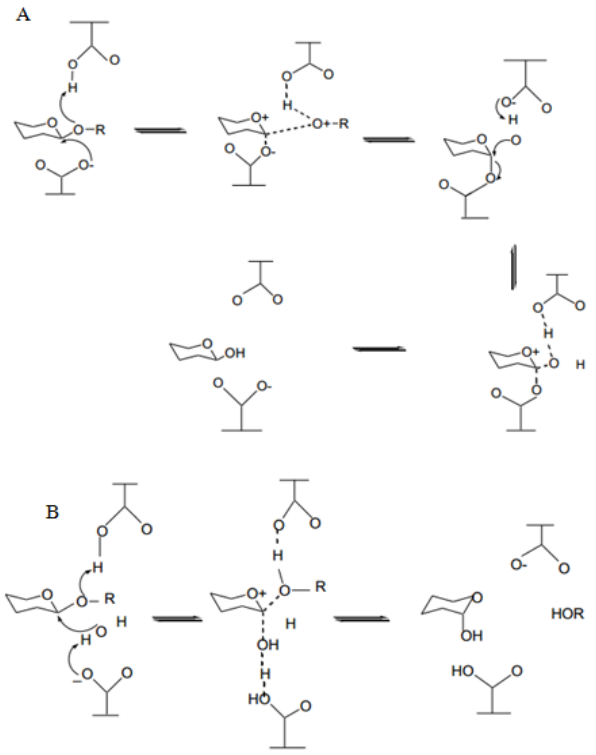

Figure 1. Mechanism of action of retaining β-glucosidase (A) and inverting β-glucosidase (B)

1.3. Mechanism of Actions of β-Glucosidase

β-Glucosidase are either retaining or inverting enzymes depending on the configuration of anomeric carbon atom of the released glucose e.g., retaining β-glucosidase cleaves β-glucosidic bond with the resulting glucose unit has β-configuration whereas in inverting β-glucosidase the resulting glucose has α-configuration. β-Glucosidase belonging to GH family 1 and 3 are retaining enzyme while those placed in GH family 9 are inverting enzymes [49]. Both inverting and retaining enzymes follow acid-base catalysis mechanism and two residues at their active site, general acid/base catalyst and nucleophile, are involved in catalysis. Retaining enzymes catalyze the hydrolysis in two steps: glycosylation and deglycosylation, or double displacement mechanisms. In glycosylation, the catalytic acid/base donates a proton to the substrate leading to formation of oxocarbonium ion, and then the nucleophile attack the anomeric carbon atom yielding enzyme-glycosyl intermediate. In the deglycosylation step, a water molecule attacks enzyme-glycosyl intermediate to displace the catalytic nucleophile from the glucose with basic assistance of the catalytic acid/base [109,110,111]. Inverting enzymes catalyze the hydrolysis of glycosidic bond in one step reaction in which a water molecule acts as nucleophile and attacks the anomeric carbon atom to displace the aglycone (Figure 1) [109]. The catalytic residues are highly conserved among glycoside hydrolase families, and clans. The nucleophile of β-glucosidase belonging to GH 3 has been identified as Asp residue which is highly conserved; while catalytic general acid/base residue appeared to be presented by different motifs in different members, although mostly it is His-Asp dyad motif in which the histidine side chain involves in catalysis [112,113,114,115]. In β-glucosidases belonging to GH family 1, the catalysis is mediated by two glutamic acid residues one acts as nucleophile and other as general acid/base catalyst [116]. For instances, in *Streptomyces* sp, a glutamic acid at position 178 acts as general acid/base catalyst while glutamic residue at position 383 acts as nucleophile [117].

2. β-Glucosidase Sources

β-Glucosidase is a ubiquitous enzyme expressed by all life domains: bacteria, fungi, plants and animals. It has been purified and characterized from animals and plants [118,119]. For the industrial utilization, microorganisms are considered the best choice for enzyme productions. The preference of microorganisms as source of industrial enzymes is attributed to many reasons such as 1) microorganisms grow rapidly speeding up the production of enzyme, 2) microorganisms are easier to handle than animals and plants since they require less space making the processes cost effective, 3) microorganisms can easily be manipulated with help of genetic engineering, mutagenesis and direct evolution and 4) furthermore, some microorganisms produce enzymes with special characteristic such as thermostablility and alkalophilicity which can be utilized in many industries requiring such harsh conditions [120,121]. β-Glucosidase is obtained from fungi and bacteria, although fungi are the preferred source of cellulase enzymes [122].

2.1. Fungal β-Glucosidase

β-Glucsidase has been produced, purified, and characterized from many fungal species majority of which are extracellular enzymes belonging to GH 3. For instance, β-glucosidase has been produced and characterized from *Trichoderma reesei* [123], the filamentous fungus *Acremonium persicinum* [124], *Aspergillus oryzae [96]*, *lanuginosus*–SSBP [125], *Thermoascus aurantiacus* [126], *Chaetomium thermophilum* var. *coprophilum* [127], *Penicillium purpurogenum* [128], *Daldinia eschscholzii [129]*, *Melanocarpus sp. MTCC 3922* [130], Neocallimastix patriciarum W5 [131], *Monascus purpureus [132]* and brown-rot basidiomycete *Fomitopsis palustris* [133]. Moreover, β-glucosidase recently has been produced from *Penicillium purpurogenum KJS506* [134], *Phoma sp. KCTC11825BP* [135], *Aspergillus fumigatus Z5* [136], *Penicillium italicum* [137], *Fusarium proliferatum* NBRC109045 [33], *Aspergillus saccharolyticus* [138,139], *Aspergillus niger A20* [140], *Fusarium solani* [141], *Flammulina velutipes* [142], *Monascus sanguineus* [143], *Sporothrix schenckii* [144], *Gongronella butleri* [145], and *Fusarium oxysporum* [146]. Although *Trichoderma reesie* is major source of industrial cellulase, it lacks sufficient amount of β-glucosidase activity for efficient cellulolysis, therefore supplementary β-glucosidase is required for efficient biomass hydrolysis. The fungal species *Aspergillus niger* is the major source of commercial β-glucosidase under the name of Novazym188 [90].

2.2. Bacterial β-Glucosidase

Although bacteria are known to secrete cellulase enzyme in lower quantities, they have been the focus of

many researchers for production of cellulases and β-glucosidase because of their high multiplication rate and robust properties exhibited by bacterial enzymes [147,148,149]. β-Glucosidase has been identified, purified and characterized from several bacterial species such as *Clostridium thermocellum [150]*, *Pyrococcus furiosus* [151], *Bacillus circulans* subsp. *Alkalophilus* [103], *flavobacterium johnsoniae* [152], *Actinomycete Thermobifida fusca* [153], *Paenibacillus* sp. Strain C5 [154], *Lactobacillus brevis* [155], *Caldicellulosiruptor saccharolyticus* [156], and *Terrabacter ginsenosidimutans* sp. [157]. Recently high glucose tolerant β-glucosidase with high specific activity toward cellobiose from *Thermoanaerobacterium thermosaccharolyticum* has been characterized [158] and β-glucosidase with ability to transform ginsenoside Re to the minor ginsenoside Rg 2 from *Pseudonocardia* sp. Gsoil 1536 has also been identified [159].

2.3. Metagenomics β-Glucosidase

Microorganisms are the most diverse and enormous living organisms on Earth, representing about 60% of the total biomass. Current research estimated that soil and oceans contains about 4–5 x 10^{30} and 3.6 x 10^{29} microbial cells, respectively [160]. Only 1% of these microorganisms are culturable by laboratory standard techniques and majority, about 99%, are unculturable under laboratory conditions, thus making them unexplored to investigation and utilization for production of many value-added products [161,162,163]. Metagenomic, a term coined by Handelsma in 1998, is culture-independent technique utilized to analyze the genetic material present in an environmental sample [164]. This approach starts with environmental DNA extraction and digestion, metagenomic DNA library construction, and screening of libraries for gene and sequences of interest [160,163,165,166]. Screening of metagenomic library can be done either by function-based screening, gene specific screening or direct sequencing [160,164,167]. Finally cloning and expression studies are carried out for the gene of interest. Metagenomic approach can be utilized for finding a novel genes encoding for novel protein e.g., enzymes with special characteristics. Numbers of β-glucosidases have been characterized using metagenomic approach from different environmental samples such *Globitermes brachycerastes* gut metagenome [168], wetland soil metagenome [169], agricultural soil metagenome [170,171,172,173], compost microbial metagenome [174], cow rumen metagenome [175], rabbit cecum metagenome [176], buffalo rumen metagenome [177], bioreactor contents metagenome [178] Kusaya gravy metagenome [179], marine metagenome library [180,181], hydrothermal hot spring metagenome [182], alkaline-polluted soil metagenome [183], amazon soil metagenome [184], cattle rumen metagenome [185], and mangrove soil metagenome [186].

3. Microbial β-Glucosidase Production

Generally microorganisms produce low amount of β-glucosidase e.g., cellulase hyperproducer species, *Trichoderma reesie*, lacks sufficient β-glucosidase activity [187,188]. Therefore, the search for microorganisms with high β-glucosidase productivity is the concern of researchers. β-Glucosidases have been produced from number of fungi, yeast and bacteria using either solid state fermentation (SSF) or submerged fermentation (SMF) [99,189,190]. In SSF, the microorganism is grown on solid substrate such as castor bean cake, sugarcane bagasse, cassava cake, wheat bran, rice straw or corn husk solely or in combination. Substrate is used steadily and slowly therefore SSF can be carried out for long period of time. SSF is more suited for cultivation of microorganisms with less moisture content requirement. The advantages of SSF are high productivity, cheap substrate utilization, low energy requirement, minimal water output and lacking of foam up, but heat generation and lacking knowledge on automation are the limitations [191,192,193]. In SMF, free flowing liquid such as molasses and broths containing different nutrients is utilized for cultivation of microorganisms. The bioactives, enzymes, and metabolic wastes are secreted into fermentation medium and the substrates are rapidly utilized therefore continuous supplementation with nutrients is needed. This fermentation technique is best suited for microorganisms that require high moisture content such as bacteria. The main advantages of SMF are the easiness of: sterility, heat and mass transfer, process monitoring and automation, and extraction and recovery of enzymes and bioactives [46,192,194,195,196,197,198]. There are several reports on β-glucosidase production from filamentous fungi, and yeast by SSF and SMF. Table 1 summarizes production methods from different microbial sources.

Table 1. Production methods of β-glucosidase from different fungi and yeast species

Fungal species	Fermentation method	Ref#
Tolypocladium cylindrosporum Syzx4	SMF	[199]
Penicillium simplicissimum H-11	SMF	[200]
Aspergillus strain SA 58	SSF	[201]
Penicillium citrinum YS40-5	SSF	[202]
Fusarium proliferatum	SMF	[33]
Fusarium solani	SSF	[203]
Aspergillus niger* + *A. Oryzae	SSF	[204]
Fomitopsis palustris	SMF	[133]
Aspergillus niger SOI017	SMF	[205]
Flammulina velutipes	SMF	[142]
Monascus sanguineus	SSF	[143]
Phoma sp. KCTC11825BP	SMF	[135]
Aspergillus niger AS 3.4309	SSF	[206]
***Aspergillus terreus* EMOO 6-4**	SSF	[207]
***Thermomucor indicae-seudaticae* N31**	SSF	[208]
***Aspergillus niger* HDF05**	SSF	[209]
Gongronella butleri	SSF	[145]
Penicillium miczynskii	SMF	[210]
Fusarium oxysporum	SMF	[146]
Yeast species		
Aureobasidium pullulans	SMF	[211]
Candida peltata	SMF	[106]
Kluyveromyces marxianus	SMF	[212]
Aureobasidium sp.	SSF+SMF	[213]
Saccharomyces cerevisiae	SMF	[214]

3.1. Production Parameters

Optimization of fermentation conditions is very crucial step for profitable enzyme production and commercialization. There are many parameters which need to be carefully optimized during fermentation processes for enzyme production. These parameters include carbon source and concentration, nitrogen source and concentration, salts, pH, temperature, oxygen availability, fermentation period, inoculum size etc. [215,216]. The optimal conditions for fermentation vary depending on microbial species, required end product (e.g., enzymes), and production methods, among others factors.

3.1.1. Carbon Source

β-Glucosidase, among other cellulases, is an inducible enzyme synthesized by microbial cells in response to various carbon sources included in fermentation medium. These carbon sources may be complex such as cellulose, wheat bran, rice straw, rice husk, sugar cane bagasse, and pectin, or simple sugar such as glucose, lactose, cellobiose, or sophorose. Complex sugar cannot enter the cells through cell membrane, it is therefore believed that some constitutively expressed enzymes degrade them to simple sugar such as cellobiose, lactose etc. which can then be transported through the cell membrane via specific transporters to the cytosol where they induces the expression of these enzymes in poorly understood mechanism [64,101,217,218]. Synthesis of β-glucosidase, and other cellulases, is repressed by metabolizable sugar such as glucose in phenomenon known as catabolite repression [213,214]. The optimal carbon source for β-glucosidase production varies depending on the species utilized for β-glucosidase production, fermentation method, and other fermentation parameters and interaction among these factors. For instances, optimum production of extracellular and intracellular β-glucosidase from *Chaetomium thermophilum* var. *coprophilum* was achieved when sugar-cane bagasse and avicel used as carbon source, respectively [127]. *Aspergillus oryzae* optimally produces β-glucosidase with high glucose-tolerance (HGT-BGL) when quercetin was used as carbon source [96]. Under solid state fermentation, *Aspergillus* strain SA 58 expressed two extracellular β-glucosidase when pectin was used as carbon source [201]. Microbial consortium implies two or more microbial groups. Optimal production of β-glucosidase from the microbial consortium of *Aspergillus niger* and *A. oryzae* was achieved when wheat bran was used as carbon source [204]. Similarly, optimum production of β-glucosidase from *Fusarium proliferatum* NBRC109045 was achieved when it was cultured on corn stover and wheat bran containing medium [33]. *Aspergillus saccharolyticus* produced an optimal β-glucosidase activity when cultivated on media containing xylose, xylan, wheat bran, and pretreated corn stover [138]. *Flammulina velutipes* and *Penicillium Purpurogenum* achieved optimal β-glucosidase production when grown on medium containing sucrose as carbon source [128,221]. Optimal β-glucosidase production from *Monascus sanguineus* was obtained when jack fruit seed was used as carbon source among wheat bran, coconut residue, tamarind seed and jack fruit seed tested [143]. *Stereum hirsutum* produced optimum β-glucosidase when it was grown on avicel followed by cellulose and minimum production was observed in glucose containing medium [222]. *Lichtheimia ramosa* produced optimal β-glucosidase activity under wheat bran as carbon source under SSF [223] and that from *Aspergillus niger* NRRL 3112 was produced optimally when wheat bran and glycerol were used as co-substrate [224]. More interestingly, an optimal production of extracellular β-glucosidase from *Candida peltata* was achieved when it was grown on glucose and xylose containing broth medium both of which are considered simple metabolizable sugar and a catabolite repressors for these genes [106]. *Kluyveromyces marxianus* produced optimal β-glucosidase when cultivated in medium containing cellobiose, sucrose and lactose [212] and *Aureobasidium pullulans* produced highest level of extracellular β-glucosidase when cultivated on medium containing lactose and corn bran [211]. Optimum production of extracellular β-glucosidase from *Proteus mirabilis* VIT117 was achieved in medium supplemented with sorbitol as carbon source [225].

Many filamentous fungi have been shown to express multiple isoforms of β-glucosidase when cultured on different carbon source [45,96]. For example, *Aspergillus niger NII-08121/MTCC 7956* expressed four isoform of β-glucosidase when it was cultivated on lactose or cellulose as carbon source while only two isoforms were found when wheat bran or rice straw was used as the carbon source [226]. Similarly, *Penicillium funiculosum* NCL1 express 4 isoforms on wheat bran, 2 isoforms on sugarcane bagasse, 1 isoform on avicel containing medium under SMF whereas no isoform was induced on salicin [227]. These isoforms may result from presence of multiple genes, differential mRNA splicing, and posttranslational modifications such as glycosylation and proteolytic digestion [228,229]. The regulatory mechanism underlying the generation of these isoforms is not clear. Further investigation are needed and which may help in designing the fermentation condition for production of most suitable isoform e.g., glucose tolerant β-glucosidase.

3.1.2. Nitrogen Source

For microbes to grow, nitrogen source must be included in the fermentation medium to synthesize amino acids, proteins, nitrogenous compounds, vitamins, nucleic acids and bioactives [121,230]. Nitrogen source can be organic or inorganic. Organic nitrogen sources can be peptone, yeast extract, beef extract, tryptone, or soybean meal. Inorganic source of nitrogen can be ammonium sulphate, ammonium chloride, ammonium hydrogen phosphate etc. For optimum β-glucosidase production, different species required different nitrogen source. Most of researchers have not reported optimization of nitrogen source for β-glucosidase production. β-Glucosidase was optimally produced from *Penicillium simplicissimum* H-11 cultivated on medium containing bean cake powder as nitrogen source [190]. *Chaetomium thermophilum* var. *coprophilum* produced optimum β-glucosidase when grown on peptone and yeast extract as nitrogen source [231]. *Aspergillus* strain SA 58 produced high level of extracellular β-glucosidase when cultured on medium containing beef extract as nitrogen source while least production was observed when ammonium salts were used

as nitrogen source [201]. *Flammulina velutipes* produced highest β-glucosidase activity when L-asparagine was used as nitrogen source in comparison to other ammonium salts which produced negligible to low activity [221] whereas *Penicillium citrinum* YS40-5 was found to produce the highest level of extracellular β-glucosidase when cultivated on urea containing medium as nitrogen source under SSF [232]. *Penicillium purpurogenum* was found to produce high level of intracellular β-glucosidase when grown on medium containing $NaNO_3$ as nitrogen source among three salt tested $NaNO_3$, KNO_3, $(NH_4)_2NO$ tested [128]. *Stereum hirsutum* produced optimal β-glucosidase when tryptone was used as nitrogen source [222]. *Kluyveromyces marxianus* produced optimal β-glucosidase when corn steep liquor was used as nitrogen source [212]. *Aspergillus protuberus* produces optimum β-glucosidase when ammonium sulfate was used as nitrogen source under SSF [233]. Similarly, the mechanism by which these nitrogen sources influence the expression of β-glucosidase is not clear and more future investigation is required.

3.1.3. Temperature

Temperature of β-Glucosidase production varies from species to species. Usually production temperature of β-glucosidase coincides with optimal temperature for microorganism growth. For instance, β-glucosidase has been produced from *Monascus purpureus* at 30°C [132], *Penicillium italicum* at 28°C [137], *Chaetomium thermophilum* var. *coprophilum* at 45°C [231], *Penicillium simplicissium H-11* at 30°C [190], *Daldinia eschscholzii* at 25°C [129], *Thermoascus aurantiacus* at 50°C [126], and *Aspergillus oryzae* at 28°C *[96]*. *Aspergillus* strain SA 58 was found to produce maximal β-glucosidase at a temperature of 35°C, although the organism grows optimally at 30°C. A temperature of 32°C was optimal for β-glucosidase production from *Penicillium purpurogenum* KJS506 which grow optimally at 28°C [134]. Optimum production of β-glucosidase from *Lichtheimia ramosa* and *A. protuberus* was obtained at 35 and 30°C when tested in a temperature range of 25-45°C and 25-40°C, respectively [223,233]. β-Glucosidase has been produced from bacterial species: *Clostridium thermocellum* at 60°C [150], archaeon *Pyrococcus furiosus* at 90°C [151], *Lactobacillus brevis* at 25°C [155], *flavobacterium Johnsonae* at 28°C [152], psychrotolerant *Shewanella* sp. G5 at 15°C [154], these temperatures are exactly the same for species growth. Most of researchers has also reported the optimization of temperature for β-glucosidase production from various species rather an arbitrary temperature usually the same for optimal growth is used.

3.1.4. pH

Different species required different initial pH for optimal production of β-glucosidase. Like in case of temperature, most researchers worked on β-glucosidase have not reported optimization of pH for β-glucosidase production rather they use an arbitrary pH at which these species grow optimally. For instance, β-Glucosidase has been produced from *Fusarium oxysporum* at pH 6 [234], *Penicillium italicum* at pH 4.5 [137], *Aspergillus oryzae* at pH 6.0 [96], *Fusarium proiferatum* NBRC109045 at pH 5.0 [33], *Candida peltata* at pH 5.0 [211], *Daldinia eschscholzii* at pH 5.5 [129], and *Phoma sp.* KCTC11825BP at pH 4.5 [135]. *Aspergillus* strain SA 58 was found to produce optimal β-glucosidase at pH 5.0 when screened from pH 3.0-9.0 [201]. *Pichia pastoris* achieved optimal β-glucosidase production at pH 7.5 when screened from pH 4-8 [235] The microbial consortium of *A. niger* and *A. oryzae* was found to produce optimal β-glucosidase at pH 5.5 when it was screen from pH 4.5 and 7 [99].

3.1.5. Incubation Time/Fermentation Period

Fermentation period is another crucial parameters affecting enzyme production. Fermentation process has to be carried out for an optimum time which otherwise optimal production of specific value-added product e.g., enzyme cannot be achieved. Usually the production of enzyme increased with increase of incubation time till it reaches an optimal peak beyond what there is a decline in enzyme production and activity. The decline in the enzyme production may be attributed to decline in the nutrient availability, accumulation and/toxicity of waste products, and decrease in the stability of the enzyme itself. Optimal β-glucosidase production from *Aspergillus niger* and *Trichoderma* sp. was achieved after 4 and 5 days of fermentation, respectively, after which the production was decreased gradually [215]. Optimum extracellular β-glucosidase production from *Penicillium purpurogenum*, and *Chaetomium thermophilum* var. *coprophilum* was achieved after 96 and 140 h, respectively [231]. Optimum production of an extracellular β-glucosidase from *Fusarium solani*, *Lichtheimia ramose*, and *Thermomucor indicae-seudaticae* was achieved at 72, 96 and 196 h on SSF [203,208,223].

In addition, number of other parameters affect the production of these bioactives or enzymes such β-glucosidase during fermentation processes. These parameters includes inoculum size, moisture content, fermentation methods, fermentation volume, fermenter size, substrate concentration, salts and its concentration, aeration, and additives. The exact mechanism by which fermentation parameters affect β-glucosidase production is not clear and it appears to be species specific and highly influenced by interaction between parameters. Future investigation should focus on understanding the mechanisms by these parameters influence the production of this valuable enzymes and the interaction between various parameters so that designing of cost effective processes may be initiated. Moreover, isolation of new microbes, fungi and bacteria, and optimization of fermentation conditions for β-glucosidase production under SSF and/SMF is highly encouraged.

3.2. Statistical Design Approach for Improvement of β-Glucosidase Production

Optimization of fermentation conditions for production of β-glucosidase is of the crucial importance because these parameters significantly affect the enzymes production, yield and productivity. Optimization is usually carried out using the traditional approach known as One Variable At a Time (OVAT) by changing one variable keeping all other factors constant. However, OVAT is not efficient method

for optimization because it ignores the interactions between different parameters which are actually independent, in addition, it is laborious, expensive and time consuming thus it usually fails to identify optimal fermentation conditions. Statistical methods such as Response Surface Methodology (RSM) is a new effective statistical method for optimization of fermentation conditions because it takes the interaction of multiple variables into consideration and reduces the number of experiments needed to be performed [207,236]. RSM has been used for optimization of 4 parameters (yeast extract concentration, cellobiose concentration, ammonium sulfate concentration, and pH) for β-glucosidase production from *Aspergillus niger* SOI017 and found that 0.275% yeast extract, 1.125% cellobiose, and 2.6% ammonium sulfate at a pH value of 3 are the optimal condition for β-glucosidase production [205]. Job *et al* optimized the fermentation condition for glucose tolerant β-glucosidase from *Paecilomyces* sp. using Plackett–Burman and Box–Behnken design revealing that peptone concentration of 2 g/l, inoculum concentration of 1.2 x 10^6 spores/ml and an incubation period of 96 h are the optimal conditions for enzyme productions [237]. El-Naggar *et al* employed two Plackett-Burman and Box–Behnken designs for optimization of β-Glucosidase production from *A. terreus* demonstrating that NaNO3, KH2PO4 and Tween 80 are the variable with maximum effect on enzyme production [207]. Mahapatra *et al* found that an optimum inoculum size, pH and yeast extract of 2 %, 9 and 2 %, respectively, are the optimum for extracellular *β*-glucosidase production from Proteus mirabilis VIT117 using Plackett–Burman and RSM statistical approaches [225].

4. β-Glucosidase Applications

β-Glucosidase is a hydrolytic enzyme that acts upon β(1-4) glucosidic bonds of disaccharides, oligosaccharides and glucose-substituted molecules. Under certain circumstances, it also catalyzes synthetic reactions through reverse hydrolysis or transglycosylation. β-Glucosidase has the potential to be used in many biotechnological applications. β-Glucosidase applications can be divided into: 1) applications based on hydrolytic activity 2) applications based on synthetics activity.

4.1. Applications Based on Hydrolytic Activity

β-Glucosidase involves in the hydrolysis of β(1-4) glucosidic linkages of disaccharides e.g., cellobiose, oligosaccharides and glucose-substituted molecules, although some novel β-glucosidase can hydrolyze bonds such as β (1-3), β (1-6), β (1-2) bonds. Therefore it can be utilized in many applications in biofuel production, food technology, and biomedical sciences.

4.1.1. Biofuel Production

Production of biofuel e.g., bioethanol, from plant biomass, involves the use of many enzymes that act synergistically to degrade the lignocellulosic material to pentose and hexose sugar which in turn is fermented to ethanol. Cellulases and xylanases are the major components' of these enzymes [238]. Cellulase enzymatic system is comprised of three enzymes, endoglucanase, cellobiohydrolyase, which degrade the cellulose chain to cellobiose and short oligosaccharide and both get inhibited by cellobiose, and β-glucosidase which hydrolyze cellobiose and oligosaccharides into glucose unit eliminating cellobiose inhibition and increasing the rate of cellulolysis. Unfortunately β-glucosidase itself are inhibited by their end-product i.e., glucose thus limiting the rate of cellulose hydrolysis therefore β-glucosidase is considered as the rate-limiting step in cellulolysis pathway and the bottle neck in biofuel production [90,239,240]. Cellulase hyperproducers filamentous fungus *T. reesei* lacks sufficient amount of β-glucosidase, which is another hurdle in biomass conversion and biofuel production [241]. Therefore majority of reported β-glucosidase identified and characterized for their biochemical and kinetics properties are meant to be utilized in biomass hydrolysis and in solving these problems associated with β-glucosidase e.g., low productivity and glucose sensitivity [90,146,242,243,244].

4.1.2. Isoflavones Glycoside Hydrolysis

Phenolic compounds (flavonoid, flavonone, flavones, and isoflavone) are a class of plants secondary metabolites differing in their chemical structures and biological functions. These compounds recently have been the focus of many researchers especially in the field of health and food technology because of their biological activity as antioxidant, anticancer, antiallergic, anti-inflammatory agents, antihypertensive etc. [245,246,247]. Naturally, majority of these compounds are presents in form of glycosides which increase their water solubility and stability and limit their absorption from human GIT [248]. Usually these glycosides contain monoglucose unit conjugated to other sugar such as galactose, arabinose, or xylose. The release of aglycone moiety requires the action of specific enzymes such as arabinosidase, and β-glucosidase. The liberated aglycone can be easily absorbed thus increasing their biological potency [249]. Numbers of β-glucosidase have been reported for hydrolysis of isoflavone or flavonoid compounds. Table 2 summarizes the sources of β-glucosidase tested on isoflavones and flavonoid compounds.

4.1.3. Flavor Improvement

In last few decades, researchers revealed that most of the flavor compounds in plants and fruit tissue are presents in form of glycoconjugate rendering them flavorless and nonvolatile compounds [265]. Glycoside flavor compounds have been reported in wide range of fruit such as grape [266,267], yellow plum [268], mango [269], and strawberry [270]. These glycosides are complex and diverse in their structures particularly aglycone moiety. Glycone part usually consist of glucose unit conjugated to various glycosides such as 6-O-α-L-arabinofuranosyl-β-D-glucopyranosides, and 6-O-α-L-arabinopyranosyl-β-D-glucopyranosides. To make these flavorless compounds available to flavor content, they must be hydrolyzed to release the aglycone part. Hydrolysis can be carried out using acids or, most favorably enzymes [271,272]. The enzymatic hydrolysis is

carried out in two sequential steps, firstly, enzymes such as α-L-rhamnosidase, or α-L-arabinosidase cleaves of the terminal sugar: arabinose and rhamnose, secondly, β-glucosidase acts upon the corresponding β-D-glucoside releasing glucose and aglycone moiety such as monoterpenol [273]. Unfortunately, β-glucosidase from plants such as grapes has low activity and unstable under wine making conditions therefore adding β-glucosidase from microbes with high activity and stability is mandatory for complete hydrolysis of flavor compounds. β-Glucosidase with high hydrolytic efficiency for terpenyl glycoside has been reported from *Sporidiobolus pararoseus* [274], and *Aureobasidium pullulans* [275] suggesting their potential application for the development of wine aroma. Another β-glucosidase from *Oenococcus oeni* ATCC BAA-1163 capable of hydrolyzing glycoside present in muscat wine has been reported [276]. Another β-glucosiadse from *Lactobacillus brevis*, lactic acid bacterium, with xylosidase, arabinosidase and cellobiosidase activities has been and was stimulated by ethanol and methanol up to 2-fold, and has have life of 50 day at pH 7.0 and 4 days at pH 4.0 suggesting the possibility of its utilization in aroma enhancement of wine [155]. *Oenococcus oeni* ST81 was found to produce a β-glucosidase with high tolerance to fructose, malate, mannitol, or sorbitol and its activity was increased by ethanol up to 147% and its half-life at pH 5.0 was 50 days making it of interest in wine making [277]. An extracellular β-glucosidase from *Issatchenkia terricola* was also found to be highly active in the presence of 18% ethanol, 10% glucose, and 6% metabisulfite with relative stability at pH 3.0. It was also immobilized on Eupergit C increasing of its stability and resulting in aromatization of white Muscat wine over a 16-day experiment increasing monoterpenes and norisoprenoids content [278]. Vervoort *et al* reported a β-glucosidase from Brettanomyces anomalus capable of methyl salicylate, linalool, benzyl alcohol, and eugenol in comparison to that from *A. niger* and Almond glucosidase [279].

4.1.4. Cassava Detoxification

β-Glucosidase has the potential to be used in detoxification of cassava. Cassava is a carbohydrate rich plants that grow in many places of the world and represent a staple food for 500 million people in the world. However, consumption of raw cassava is harmful to human health due the presence of cyanogenic glycoside such as linamarin and lotaustralin [280]. Moreover, a correlation between human central nervous system syndrome “Konzo” and prolonged consumption of cassava products has been established. Naturally cassava is detoxified during processing and grating by endogenous β-glucosidase and linamarase present in the root. However, these enzymes are expressed insufficiently leaving part of cyanogenic glycosides in the processed food. It is therefore suggested that an exogenous linamarase and β-glucosidase from microbial sources can be utilized to enhance the hydrolysis of cyanogenic glycoside from this important food [75,280,281,282,283].

Table 2. List of microbial sources of β-glucosidase based on the ability to hydrolyze flavonoid compounds

Source of BGL	Flavonoid glycoside	Product	Biological activity	Ref
L. acidophilus LA-5	Delphinidin-3-glucoside Malvidin-3-glucoside	Gallic, Syringe homogentisic acid	Antioxidant	[250]
Paecilomyces thermophila J18	Daidzin, Genistin, Glycitin	Genistein, Daidzein, Glycitein	Anticancer, Osteoporosis Antihypercholesterolemia	[251]
Thermoanaerobacter ethanolicus JW200	Daidzin, Genistin	Genistein Daidzein	Anticancer Antipostmenopausal syndrome	[252]
Pseudomonas ZD-8	Genitin and Daidzin	Genistein Daidzein	Anticancer Osteoporosis etc.	[253]
Bacillus subtilis 18,	Genistin Daidzin	Genistein Daidzein	Anticancer Osteoporosis etc.	[254, 255]
Gongronella sp.	Daidzin Genistin,	Daidzein, Genistein,	Anticancer Osteoporosis	[256]
Saccharomyces cerevisiae HJ-014	Gensin	Ginsenoside Rd, F2 Compound K (CK)	Anti-inflammatory Anti-cancer Anti-aging, Antioxidant activities	[257]
Paecilomyces Bainier sp. 229	Ginsenoside Rb1	Compound K	Tonic, Adaptogenic, Immunomodulatory, Anti-aging effects	[258]
Mucilaginibacter sp	Protopanaxatriol-type ginsenoside mixture (PPTGM)	(*S*)-Rh1 (*S*)-Rg2	Antineoplastic, Antistress Antioxidant activities	[259]
Paenibacillus sp. KB0549	2,6-O-di(β-D-glucopyranosyl)-β-D-glucopyranosylsesaminol (STG)	Sesaminol	Antioxidants	[260]
Pyrococcus furiosus	Hesperidin, Neohesperidin, Naringin, Poncirin, Diosmin Neoponcirin, Rutin	Hesperetin, Hesperetin, Haringenin, Naringenin, Quercetin, Rutinose	Antiallergic, Antioxidant, Anti-inflammatory, Antihypertensive	[261]
Bifidobacterium bifidum	Daidzin, Genistin,	Daidzein Genistein	Anticancer, Osteoporosis Antihypercholesterolemia	[262]
Bacteroides thetaiotaomicron VPI-5482	Daidzin, Genistin, Glycitin	Daidzein Genistein Glycitein	Anticancer, Osteoporosis Antihypercholesterolemia	[263]
Aspergillus terreus	Daidzin, Genistin, Glycitin	Daidzein Genistein Glycitein	Anticancer, Osteoporosis Antihypercholesterolemia	[264]

4.1.5. Dinking of Waste Paper

Paper and pulp industry is one of the most wood consumer industries, and is expected to be expanded more due to increase in the world economy and population. Waste paper is one of the major environmental pollutants. Recycling of waste paper is attracting more attention in the current time to solve this two-dimensional problem: forest wood consumption and landfills pollution. Recycling of waste paper can be carried out by chemical or enzymatic method. The major hurdle to waste paper recycling is the removal of ink. Removal of ink from waste paper by conventional methods utilizes several chemicals which are environmentally harmful and decrease in the brightness of the paper. The enzymatic method for waste paper recycling has been reported to be efficient in solving these problems. The enzyme preparations for waste paper recycling contain cellulase, β-glucosidase and hemicellulase [77,284,285,286,287].

4.2. Application Based on Synthetic Activity

β-Glucosidase is known to have synthetic activity other than hydrolytic activity, namely transglycosylation and reverse hydrolysis resulting in the synthesis of a variety of oligosaccharides, aryl- and alkyl-β-D-glycosides with wide range of applications. Synthesis of oligosaccharides by β-glucosidase is preferred over glycosyl transferase because of their higher regio- and stereo-selectivity. Moreover, synthesis of these compounds by β-glucosidase does not require any input energy in form of sugar nucleotides as is the case of glycosyl transferases [288]. Alkyl glycosides have a wide range of applications since they are biodegradable nonionic surfactants owning good emulsifying and antimicrobial properties imparted by their carbohydrate head group [102,289,290]. N-alkyl glucoside ester formed by reaction of phenyl butyric acid and n-alkyl butyl glucoside by β-glucosidase –lipase are used in treatment of fever [291]. On other hand, synthetic oligosaccharides can be utilized in various applications: 1) therapeutics agents such as Heparin and Acarbose, 2) carbohydrate based techniques such as antibacterial, anti-parasite and antiviral vaccines, and 3) probiotic agents since they enhance the growth of beneficial microorganisms in human gut flora [84,288].

5. Conclusion Remarks

β-Glucosidase is an important component of cellulase system produced by all life domains playing fundamental roles in many life processes. β-Glucosidase, as of cellulase system, it eliminates cellobiose inhibition on endoglucanase and cellobiohydrolase during cellulose hydrolysis facilitating biomass hydrolysis. It also hydrolyzes different β-D-glucosides compounds and, under certain circumstances, has synthetic activity through reverse hydrolysis and transglycosylation. Therefore, it has wide spectrum of applications exemplifying by biofuel production, food technology and biomedical sciences. β-Glucosidase is produced by microorganisms in low quantities, and inhibited by its end-product i.e., glucose limiting its application in biomass hydrolysis and biofuel production. Therefore, upcoming research should focus on finding novel microorganisms with high β-glucosidase production efficiency and β-glucosidase with high catalytic efficiency, thermostability and glucose-tolerance. It is also of great importance to study the structure of these enzymes at molecular level and *in silico*, and to identify those amino acids involving in the catalysis and glucose tolerance so that protein engineering techniques may be employed to design a β-glucosidase with high catalytic activity and glucose tolerance making biomass hydrolysis cost effective and profitable.

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